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CHAPTER

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Physical Activity and Upper Respiratory Infection

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I. INTRODUCTION

Interest in the influence of physical activity on resistance to infectious disease has been stimulated by recurring reports that whereas moderate training enhances immune responses, excessive amounts of exercise—whether a single marathon run or a period of excessive training leading up to international competition—can suppress immune function for several hours to a week. The impact upon personal health of such changes in the immune response has been a source of controversy for many years (Cannon, 1993). Many exercise scientists now believe that although susceptibility to bacterial infections remains unaltered, the affected individual is at increased risk of upper respiratory infections (Brenner, Shek, & Shephard, 1994; Nieman, 1994; Gabriel & Kindermann, 1995; Peters-Futre, 1997). Others still argue that special factors associated with high-performance competition give a false impression of an increased vulnerability to viral infections (Cannon, 1993).

This chapter summarizes normal mechanisms of defense against acute viral infections and considers briefly how protection may be modified by participation in acute and chronic physical activity. It then examines empirical epidemiological evidence suggesting an altered susceptibility to upper respiratory infections after participation in various types of exercise and training programs. Possible causes of spurious associations are explored, and the modulating influence of environmental factors, including psychological stressors, is discussed. Finally, brief comment is offered regarding the prevention and treatment of exercise-induced immunosuppression.

II. NORMAL MECHANISMS OF DEFENSE AGAINST VIRAL INFECTIONS

The body offers both physical/mechanical and biological barriers to viral infection (Table I); both of these may be compromised if a person engages in heavy physical activity (Shephard, 1997).

A. Physical and Mechanical Barriers

Susceptibility to any viral particles, which are suspended in the inspired air, depends on patterns of respiratory airflow and the mechanical barriers

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TABLE I Normal Mechanisms of Defense against Invading Viral Infections

Physical and mechanical barriers
1 Nasal filtration
2 Mucus secretion and expectoration
3. Endothelial membrane
Biological barriers
1 NK cells
Lysis of infected cells
2 Interferon
Enhanced NK cell activity
Inhibition of viral replication
3 Specific antibodies
Prevention of membrane penetration by virus
Opsonization of virus
4 Cytotoxic lymphocytes
Lysis of infected cells
5 Phagocytes
Phagocytosis, presentation of viral protein to CD4+ cells
6. Complement and acute phase protein
Attraction of phagocytes to infected area
Increase of viral susceptibility to lysis

imposed by mucus and endothelium. The turbinate bones create a turbulent airflow through the nasal passages, and this tends to precipitate any larger suspended particles in the nose. However, because of their small average size, virus-containing droplets tend to remain in suspension. The endothelium lining the airways functions as a physical barrier. Its effectiveness is enhanced because of mucus secretion by the goblet cells. The tracheal ciliae cause a steady flow of mucus to the throat, where it is either swallowed or expectorated. Coughing and sneezing supplement the effects of ciliate motion.

B. Biological Barriers

The body's immediate biological response to infection is an acute inflammation of the affected tissue. Increases in local blood flow and vascular permeability facilitate the entry of leukocytes and plasma proteins into the affected region of the body. The immediate innate mechanisms available to counter viral infections include natural killer (NK) cells, phagocytes, and secretory IgA present in nasal and bronchial mucus.

NK cells have the ability to lyse infected cells and/or secrete toxic molecules onto their surface in the absence of major histocompatibility complex (MHC) proteins or cytokine messengers. Nevertheless, various cytokines, particularly interferon (IFN)-γ, a substance that also inhibits viral replication, enhance NK-cell activity. Phagocytes ingest viral particles, subsequently destroying them with potent enzymes and chemicals. Soluble elements such as complement and acute-phase protein play a supportive role, attracting phagocytes to the infected region and rendering the viral particles more vulnerable to lysis. Specific antibodies also contribute to early protection, either by preventing the virus from penetrating the endothelial cell membrane or by opsonization (a process that facilitates subsequent phagocytosis of the viral particle).

The main basis of biological defense against viral infections is the proliferation of specific cytotoxic lymphocytes. This process peaks some 7 days after the onset of infection. It depends on a sequence of events that includes macrocytic phagocytosis, killing of the microorganism by lysozymes and/or oxidizing agents, a processing of viral surface proteins, their presentation to T cells in association with MHC-restricted protein, and the secretion of various cytokines (particularly interleukin-1 and IFN-α). B cells, antibodies, and complement also act against certain viruses.

III. IMPACT OF ACUTE AND CHRONIC PHYSICAL ACTIVITY ON BARRIERS TO INFECTION

The effectiveness of both physical/mechanical and biological barriers to viral infection is modified during and immediately following a single bout of strenuous physical activity. Defenses may also be compromised by a period of heavy training such as preparation for international competition.

A. Changes to Physical and Mechanical Barriers

The high respiratory flow rates that are developed during vigorous physical activity lead to a progressive cooling and drying of the respiratory mucosa in certain climates. The movement of the endothelial ciliae is slowed, and the viscosity of the mucus is increased. Both ciliary function and expectoration are impaired, reducing the rate of clearance of pathological microorganisms from the respiratory tract. Furthermore, drying and cooling of the endothelium may adversely affect the function of mucosal B cells, reducing the local secretion of antibodies.

Above a critical threshold intensity of exercise, the effects of a large respiratory minute volume are exacerbated by the onset of mouth breathing. The normal air warming, humidifying, and filtering mechanisms of the nose are then largely bypassed. The tracheal

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mucosa becomes exposed more directly not only to cold, dry air but also to respiratory pathogens, other particulate matter, and air contaminants. We might expect these various physical and mechanical factors to increase susceptibility to both viral and bacterial infections during vigorous exercise. In practice, there is little evidence of increased susceptibility to bacteria, so we must conclude that changes in barrier functions are not a major cause of the increased risk of upper respiratory infection which has been observed in heavy exercisers. This verdict is reinforced by the fact that increased susceptibility to viruses seems contingent on undertaking a volume of exercise equivalent to a marathon run; a run of 20–30 km, which might have an almost equal impact on physical barriers to infection, does not seem to modify the body's defenses.

B. Changes in Biological Defense Mechanisms

The main basis for any change in susceptibility to upper respiratory infection seems an exercise-induced modulation of either nonspecific or specific immune defences. Regular moderate physical activity appears to enhance the efficacy of these biological mechanisms, whereas a bout of very heavy exercise or a period of intensive training weakens their effectiveness. Based on limited immunological and epidemiological evidence, several authors have proposed that the resistance to infection follows a J-shaped response curve, with excessive amounts of exercise creating a "window of opportunity" when viruses can become established in the body.

Given the normal mechanisms of biological defence outlined above, factors that might decrease the resistance to viral disease include: (1) a decrease in the number and/or function of natural killer cells; (2) a delayed or a reduced production of interferon; (3) a decreased availability of specific antibodies; (4) a decrease in the CD4+/CD8+ ratio; (5) an impaired lymphocyte proliferative response to mitogens; and (6) secondary infection due to impaired neutrophil function

1. *Natural Killer Cells*

A bout of vigorous exercise induces an acute increase in circulating NK cell count, usually with a matching rise of cytolytic activity (Shephard, 1997). The immediate rise in NK-cell numbers is correlated with the increase of heart rate, and it can be mimicked by injections of catecholamine:norepinephrine during moderate exercise, and epinephrine with more intensive effort. The primary mechanism is probably a demargination of cells, secondary to an altered expression of adhesion molecules, but the exercise-induced increase in cardiac output may also play some role (Shephard, 1997).

Catecholamine secretion may lead not only to an overall increase in circulating NK-cell count, but also to the demargination and recruitment of NK cells with a high interleukin-2 response capacity. In theory, both changes might enhance cytolytic activity and thus the body's resistance to viral infection. However, in practice, the usual duration of an exercise bout and thus the period when NK count is increased is too brief to have any substantial influence on susceptibility. Moreover, if exercise is prolonged for several hours, the NK cell count and cytolytic activity gradually return toward initial resting values, even as activity continues (Shephard & Shek, 1999).

Both NK cell counts and cytolytic activity quickly fall below normal levels once exercise has ceased. In many studies, normal resting levels of NK cell function are restored within a few hours, leaving only a brief "window of opportunity" for a marauding virus. It is hard to imagine how 2–3 h of reduced NK-cell activity could account for a two- to sixfold increase in the incidence of upper respiratory infections (Nieman, 1994) that some have described following a marathon or ultramarathon run. Nevertheless, a few authors have described longer-lasting exercise-induced depressions of NK cell counts and/or cytolytic activity (Shephard & Shek, 1999). Shek, Sabiston, Buguet, and Radomski (1995) reported the most dramatic effect. In their study, both NK counts and cytolytic activity were still substantially depressed 7 days following a single 90- to 120-min bout of exercise at 65% of the individual's aerobic power. Such a prolonged change in NK cell function could limit cytolysis over the entire period when the NK cells are expected to play a dominant role in defending the body against microorganisms; in such circumstances, a substantial increase in the individual's risk of developing an acute viral illness might be anticipated, particularly if exposure to the pathogen followed closely upon the exercise bout.

Candidate hypotheses for the suppression of NK-cell activity following vigorous exercise include a lack of interleukin (IL)-2 and an accumulation of prostaglandins (Shephard, 1997). The first explanation can be discounted, since the addition of recombinant IL-2 to isolated NK cells postexercise does not restore their cytolytic activity. On the other hand, various prostaglandins (PGE_1, PGE_2, PGA_1, and PGA_2) are known to inhibit the cytotoxic activity of NK cells. In the context of heavy physical activity or excessive

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training, the most likely explanation seems an increased PGE_2 production induced by muscle trauma.

Repeated bouts of moderate exercise can increase the NK-cell count (Shephard, 1997) and this could explain why habitual exercisers sometimes have an increased resistance to infection.

2. *Interferon*

Any exercise-induced changes in the concentrations of interleukins and interferons could exert a direct effect on viral replication and also could alter the surface properties of the NK cells, changing their lytic activity (Mackinnon, 1992). However, a delayed or decreased production of interferon seems an unlikely explanation of increased viral susceptibility. Indeed, moderate physical activity may increase IFN production, and the output of IFN-α is unchanged by several weeks of exhausting exercise (Shephard, 1997).

3. *Immunoglobulins*

Concentrations of salivary IgA and serum IgG are essentially unchanged by a bout of moderate physical activity. In contrast, very vigorous physical activity can decrease the concentration of IgA in both saliva and nasal washings. Salivary concentrations remain depressed even after correction of data to a common salivary protein concentration and thus a constant output of saliva. One report found that concentrations remained low for 18 h following a 31-km race (Shephard, 1997).

Moderate training may increase salivary IgA concentrations, but in general, the response to an acute bout of exercise is independent of initial physical condition. IgA levels fall progressively in international competitors as they increase the intensity of their training. Partial recovery is seen during precompetitive tapering. The heavy training schedules of top competitors may also cause minor decreases in serum IgG concentrations (Mackinnon, 1996) and there have been suggestions that international athletes can profit from the administration of exogenous immunoglobulins (see below).

Decreases in mucosal IgA concentrations could have an important influence on susceptibility to upper respiratory infections in the first few hours after viral exposure, given that secretory IgA inhibits attachment of the virus to the respiratory epithelium, penetration of the epithelial cells, and subsequent intracellular replication. In support of the practical significance of changes in IgA levels, several studies have noted a temporal link between decreases in salivary IgA concentrations and an increased prevalence of upper respiratory infections (Mackinnon, 1996). In one such study, 92% of athletes who developed upper respiratory infections had low secretory IgA concentrations 2 days before developing clinical manifestations of illness.

4. *CD4+/CD8+ Ratio*

An appropriate CD4+/CD8+ ratio is important to both mitogen-induced lymphocyte proliferation and viral resistance. A decrease in the ratio leads to a downregulation of several immune responses. Decreases in CD4+ count limit the output of cytokines that activate NK and T cells and stimulate the proliferation and maturation of B cells; the immediate consequences include a decrease in cytotoxic activity and a lesser production of immunoglobulins. The CD4+/CD8+ ratio may drop below the critical value of 1.5 in response to a bout of maximal exercise, a longer period of submaximal exercise, or a spell of excessive training (Shephard, 1997). Monitoring of the CD4+/CD8+ ratio may thus help to identify athletes who have pursued training to the point where their vulnerability to infection is increased.

Nevertheless, inferences which are based on the CD4+/CD8+ ratio alone can be misleading. The CD4+/CD8+ ratio may be decreased for 1 to 2 h following vigorous exercise, but at the same time there may be increases in the absolute numbers of both CD4+ (T-helper) and CD8+ (T-cytotoxic/suppressor) cells. Further information is needed regarding the importance of the absolute CD4+ count as opposed to the CD4+/CD8+ ratio. It also remains unclear how far an increase in CD4+/CD8+ ratio and thus a greater activation of NK cells can compensate for a decrease in NK cell numbers (and vice versa).

5. *Mitogen Responsiveness*

Cell proliferation and the generation of specific cytotoxic lymphocytes offer the main basis of long-term defense against viral infections. Thus, it seems important that a bout of heavy physical activity or prolonged and rigorous military training can reduce the proliferative response of peripheral blood mononuclear cells (PBMCs) to both mitogens and antigens (Shephard, 1997). This effect of an acute bout of exercise sometimes persists for several hours, contributing to the overall window of opportunity for viral infection. On the other hand, a training program can diminish the depression of mitogen responsiveness initially associated with a given acute exercise challenge.

It has been suggested that the normal proliferative response to IL-2 is suppressed by high postexercise

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concentrations of prostaglandin. However, we have been unable to normalize lymphocyte proliferation by adding various quantities of IL-2 to isolated PBMCs (Shephard, 1997).

6. *Impaired Neutrophil Function*

Upper respiratory tract infections are often complicated and prolonged by secondary bacterial infections. A dramatic increase in the circulating numbers of neutrophils is seen during and immediately following exercise, but this does not necessarily lead to an increase in phagocytosis and thus greater resistance to bacterial infection. One study found that a 20-km race doubled the neutrophil count, but at the same time the percentage of phagocytosing cells was reduced to 49% of normal, so that there was little net change in neutrophil activity. Other investigators have described reductions in neutrophil adherence and phagocytosis following heavy exercise (Lötzerich, Wilczkowiak, Stein, & Peters, 1997; Shephard, 1997).

Evidence from training studies also suggests that activity-induced changes in neutrophil function do not have great importance in terms of upper respiratory infections. For example, an Australian investigation found that the oxidative burst of isolated neutrophils was reduced following 12 weeks of intensive training, but this did not increase susceptibility to respiratory infections.

7. *Other Possible Factors*

Other acute exercise-induced changes in immune function that could influence susceptibility to upper respiratory infection include increases in C-reactive protein and decreases in resting levels of serum complement and C-reactive protein (Shephard, 1997).

8. *Overall Responsiveness to Vaccines*

Very heavy exercise can impair the overall response to vaccines. Thus Bruunsgaard et al. (1997) noted a reduced response to tetanus and diphtheria toxoid, as well as to purified pneumococcus polysaccharide in the first few days after participation in an ironman triathlon.

IV. PHYSICAL ACTIVITY AND THE RISK OF UPPER RESPIRATORY ILLNESS

Interactions between physical activity and susceptibility to infection are complex, depending on (among other factors) the type of viral challenge, the quality and quantity of the physical activity undertaken, its timing relative to the course of the disease process, and the level of other environmental and psychological stressors.

Participation in a program of regular moderate physical activity seems to reduce the risk of upper respiratory infections in both animals and human subjects. On the other hand, both anecdotal reports and clinical studies suggest that a single bout of exhausting exercise or a period of very heavy physical training may have a detrimental effect on resistance, particularly if activity is undertaken during the infectious stage of the illness.

A. Experimental Data

Limited data obtained in laboratory animals support the view that whereas moderate exercise has a beneficial effect, an excessive and/or "stressful" dose of exercise weakens host resistance to an experimental viral infection. Moreover, heavy physical activity seems to increase the virulence of certain viruses. For example, mice that have been inoculated with the influenza virus show an increased mortality if they are forced to swim during the early stages of infection (Ilbäck, Friman, Beisel, Johnson, & Berendt, 1984). Likewise, fatiguing treadmill exercise increases mortality and decreases the time to death in mice which have been inoculated with herpes simplex virus (Hertler, Davis, Kohut, Ghaffar, & Mayer, 1995).

An early human study administered filtered nasal secretions containing respiratory viruses to volunteers who were then exercised on the treadmill. Details of the exercise bout are scant, but it was concluded that the resulting fatigue caused an "insignificant" increase in the frequency with which colds were observed (Jackson et al., 1960). A more recent study instilled nasal drops containing one of five respiratory viruses or a placebo. The incidence of subsequent infection was correlated with indices of psychological stress, but was unrelated to a composite physical activity score based on walking, jogging, running, swimming, aerobic exercise, and domestic chores (Cohen, Tyrrell, & Smith, 1991). A further laboratory study assessed the severity of an experimental rhinovirus infection in terms of symptoms and the volume of mucus secreted; moderate exercise (40 min at 70% of the heart rate reserve three times per week) did not change the duration or the severity of the illness (Weidner et al., 1997).

B. Human Epidemiological Data

Human epidemiological data support the view that whereas moderate amounts of physical activity either have no effect or reduce susceptibility to upper

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respiratory infection, prognosis is worsened once the volume of activity exceeds a specific threshold. Moreover, there is some indication of a dose–response relationship between the volume of physical activity that has been undertaken and the increase in susceptibility to respiratory viruses, suggesting that the observed adverse association is causal in nature (Table II).

1. *Moderate Exercise*

A single bout of moderate physical activity has little influence on immune responses. Some authors have found that participation in a program of regular, moderate physical activity has a protective effect against viral disease, although, perhaps because old people have a poorer initial immune function and a lower average initial level of physical activity, the benefit has been most obvious in seniors.

Osterback and Qvarnberg (1987) found no difference in the incidence of infections between children who participated in extracurricular activities (gymnastics, swimming, and ice hockey) and other elementary students who were physically less active, including those who were enrolled in a music program. Possibly, the intrinsic level of physical activity in young children already reaches the minimum threshold for optimal protection against viral disease.

Schouten, Verschuur, and Kemper (1988) observed a negative correlation between the incidence of respiratory tract symptoms and a moderate level of sports participation in young adult women. However, when data for young men were included in the sample, there was no longer any significant relationship between the frequency of upper respiratory complaints and either maximal oxygen intake or the dose of exercise (a moderate average of 700 MET · min per week).

Nieman et al. (1990) noted that 45 min of exercise, five times per week at 60% of the heart rate reserve, reduced the duration of symptoms but did not affect the incidence of upper respiratory infection in a group of women ages 25 to 45 years. On the other hand, among women ages 67 to 85 years, the incidence of upper respiratory tract infections was lowest in a highly conditioned subgroup, was at an intermediate level in a subgroup of regular walkers, and was greatest in calisthenic and control subgroups (Nieman et al., 1993). Likewise, Karper, and Boschen (1993) reported that 50 to 60 min of moderate exercise, performed 3 days per week, decreased the likelihood of respiratory tract infections in women ages 60 to 72 years.

2. *Heavy Exercise and/or Overtraining*

There now is a strong consensus that heavy exercise and/or overtraining increases the risk of respiratory symptomatology. However, few investigators have obtained clinical confirmation of infection or have looked for associated changes in immune function.

Douglas and Hanssen (1978) found that university rowers reported respiratory symptoms more frequently than nonathletic controls. The athletes also perceived their symptoms as being more severe. Linde (1987) noted that orienteers reported a higher incidence of respiratory infections (2.5 episodes per year) than nonorienteers (1.7 episodes per year). Symptoms also were said to persist marginally longer in orienteers than in controls (an average of 7.9 vs 6.4 days). Seyfried, Tobin, Brown, and Ness (1985) found overall morbidity rates of 7% in recreational swimmers, compared with 3% in control subjects. The swimmers had more complaints for each of the potential routes of infection (respiratory, gastrointestinal, eye, ear, and skin), although the most frequent reports were of respiratory ailments.

Peters and Bateman (1983) examined symptoms in the 2 weeks following participation in an ultramarathon event. During this time, 33% of the runners reported respiratory symptoms, compared with 15% of the nonrunners. In those who took 5.5 to 6.0 h to cover the 56-km distance, there was only a small increase in the likelihood of upper respiratory symptoms; but the prevalence of complaints increased progressively with running speed to reach three times control in those who had completed the event in less than 4 h. Nieman, Johanssen, and Lee (1989) also observed that, on average, a group of runners who participated in a 42-km marathon race had five times the likelihood of reporting an upper respiratory illness as equally trained runners who, for various reasons, had not participated in the event. On the other hand, participation in less demanding 5- to 21-km "fun runs" had no apparent impact on the incidence of respiratory infections.

Heath et al. (1991) found that the likelihood of developing a respiratory infection over a 12-month period was related to the individual's weekly running mileage in a dose-dependent manner. Risk factors included running more than 15 km per week, living alone, and a low body mass index. Likewise, Nieman, Johanssen, Lee, and Arabatzis (1990) found that marathon runners who trained over a distance of more than 97 km per week had twice the likelihood of developing upper respiratory complaints than those who ran less than 32 km per week, even after their

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TABLE II Epidemiological Studies Examining the Influence of Acute and Chronic Physical Activity upon Susceptibility to Upper Respiratory Infections[a]

Author	Population	Type of exercise	Upper respiratory infections
Moderate exercise			
Osterback and Qvamberg, 1987	76 M/61 F, 11–14 years	Interview sports involvement	No difference from controls
Schouten et al., 1988	92 M/107 F, 20–23 years	Questionnaire activity level & fitness	No effect in males, symptoms of URI less in active females
Nieman et al , 1990	36 F, 25–45 years	45 min at 60% HR reserve 5 days/week	Reduced duration of URI symptoms
Karper and Boschen, 1993	6 M/10 F, 60–72 years	Moderate exercise 3 days/week	Reduced number of infections relative to initial state
Seyfried et al., 1985	8000 M and F, all ages to 70 years	Recreational swimming	Increased URI relative to nonswimmers
Nieman et al , 1993	44 F (elderly)	Walking 37 min 5 days/week	Reduced incidence of URI relative to controls
Weidner et al , 1997	34 M and F; 18–29 years	40 min at 70% HR reserve 3 days/week	No change in duration or severity of experimental URI
Strenuous exercise			
Douglas and Hanssen, 1978	61 Rowers and 126 cadets	University rowing	Increased frequency and severity of URI in rowers
Strauss et al , 1988	87 M	University athletics	86% report URI over 8 weeks
Peters and Bateman, 1983	145 M/5 F, 18–65 years	Ultramarathoners vs non-runners	URI symptoms increased in faster runners
Linde, 1987	55 M/28 F, 19–34 years	Orienteers vs nonorienteers	Incidence and duration of URI greater in orienteers
Nieman et al , 1990	2311 M and F, 35–37 years	Marathon runners	URI sixfold increase in faster runners after race
Heavy training			
Nieman et al , 1990	2311 M and F; 35–37 years	Marathon runners	URI twofold increase with training
Heath et al , 1991	447 M/83 F, 13–75 years	Distance running	URI increased if > 15 km/week
Lee et al , 1992	96 Air Force cadets	Initial training	Immune function depressed but no change in URI
Linenger et al , 1993	482 M	Special warfare training	High incidence of URI
Shephard et al , 1995	551 M/199 F, 40–81 years	Masters athletes	URI increased in 16% if > 70–80 km/week
Verde et al , 1992	10 M	Runners, 3-week 38% increase of training	Respiratory symptoms in 3/10

Note M, male, F, female, HR, heart rate, URI, upper respiratory infections

[a]For details of references not listed in the bibliography, see Brenner et al. (1994)

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data had been adjusted for the potential confounding influences of age, stress, and illness at home.

Shephard, Kavanagh, and Mertens (1995) questioned Masters athletes (age-classified older competitors). The majority of subjects (76%) considered themselves less vulnerable to colds than their sedentary colleagues, and only 1.5% thought they were more vulnerable. Nevertheless, the vulnerable individuals were found primarily among the endurance competitors. Moreover, some 16% of the sample were conscious of a mileage at which their susceptibility was enhanced; usually, problems did not develop until they were covering a weekly distance of 70 to 80 km.

Heavy military training has also been reported to increase the incidence of respiratory infections (Linenger, Fink, Thomas, & Johnson, 1993) with a reduction of in vitro immune responsiveness (Lee, Meehan, Robinson, Mabry, & Smith, 1992). However, other investigators have maintained that in some categories of athlete (cross-country skiers, gymnasts, oarsmen, swimmers, and wrestlers) upper respiratory infections occur no more frequently than would be expected in sedentary people (Strauss, Lanese, & Leizman, 1988; Budgett & Fuller, 1989; Berglund & Hemmingson, 1990). Presumably, much depends on the type and volume of training that the individual currently is undertaking.

V. POSSIBLE CAUSES OF SPURIOUS ASSOCIATIONS

Data suggesting that moderate physical activity protects against viral infections, but that very strenuous exercise has an adverse effect on susceptibility, are in accord with our current understanding of the responses of the immune system to various volumes of physical activity. Nevertheless, it remains important to exclude extraneous influences that could cause spurious associations between a bout of strenuous exercise and decreased resistance to infection.

Weidner (1994) has argued that for reports to be accepted, there should be a clear definition of physical activity, individual assessment of activity patterns using a reliable and valid measuring instrument, clear details of the dose of exercise (frequency, intensity, and duration), an assessment of prior activity and program adherence, and a detailed evaluation of symptoms. Few of the available reports satisfy all of these important criteria.

Critical issues that raise the specter of spurious associations include an altered exposure to pathogens, inappropriate diagnostic criteria, effects secondary to nutritional disturbances or muscle injury, and the impact of environmental and psychological stressors.

Through linkages between the hypothalamus and the immune system, a variety of environmental and psychological factors modulate the impact of acute and chronic physical activity upon the immune defenses against viral infection. Moreover, because of the pressures that surround international competition, both environmental and psychological challenges may be more severe in athletes than in laboratory subjects who perform exercise at similar relative intensities.

A. Exposure to Pathogens

The locale of competition and any associated air travel may not only increase an individual's range of exposure to infected individuals, but also bring an athlete in contact with microorganisms which have not been encountered previously. Thus, the incidence of infection may be increased during and immediately following an international competition, even if an individual's inherent susceptibility to disease remains unchanged.

B. Diagnostic Criteria

Infants and young children sustain four to eight upper respiratory infections per year, but in young adults, the annual incidence is often only one to two episodes per person. Thus, in order to look for exercise-induced changes in susceptibility to such infections, it is necessary to examine large populations.

In many epidemiological studies, the diagnosis of respiratory illness has been based on questionnaire responses rather than on detailed clinical examination. The symptoms associated with an upper respiratory infection (soreness of the throat and nasopharynx, nasal catarrh, and cough, with minimal fever) unfortunately are nonspecific, and they are easily confused with other consequences of vigorous exercise—particularly the respiratory irritation, coughing, and bronchospasm which may be caused by exposure to chemically polluted, cold, or dry air. For example, Schwellnus, Kiessig, Derman, and Noakes (1997) found a substantial reduction of upper respiratory symptoms following the topical administration of an anti-inflammatory agent (Fusafungine) as an oral and nasal spray.

The percentage of questionnaires that are returned is also rather low—for instance, 47 percent in the study of Nieman et al (1990)—and it may be that the likelihood of response to a large-scale survey is biased in favour of those who develop an infection, or who fear doing so.

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At the collegiate level of competition, only about one-third of upper respiratory infections are reported to a physician (Weidner, 1994). However, top-level athletes have ready access to medical services, and they perceive even a minor illness as limiting their competitive performance. Relative to the general public or even a collegiate athlete, they are thus more likely to report upper respiratory illnesses and to demand medical treatment for them. The decision to seek medical advice also depends heavily on an individual's perceived state of health. The anxiety associated with participation in an international competition or deterioration in performance subsequent to a period of overtraining tends to worsen perceived health. In consequence, the likelihood that an athlete will seek a medical consultation around the time of competition is further increased, even if the prevalence of organic disease is unchanged. This, in turn, could create a spurious association between high level competition and the prevalence of viral illnesses.

C. Disturbances of Nutrition

Nutritional deficiencies are a well-recognized cause of impaired immune function in clinical malnutrition. An athlete shows much smaller deficiencies of essential nutrients than the person with clinical malnutrition, but may nevertheless fail to satisfy the demands imposed by either a single bout of prolonged physical activity or a repeated depletion of glycogen stores. Newsholme (1994) pointed out that glycogen depletion is followed by a 10–20% decrease in plasma glutamine levels, and he suggested that this glutamine deficiency might be sufficient to limit the rapid proliferation of immune cells. A recent report found low plasma glutamine levels (<450 μmol/L) in all 11 of 51 top athletes who developed upper respiratory infections (Kingsbury, Kay, & Hjelm, 1998).

Other authors have suggested that deficiencies of arginine, L-carnitine, essential fatty acids, vitamin B_6, folic acid, vitamin E, and trace elements such as zinc, magnesium, and copper all contribute to an impairment of immune function in the athlete (Shephard & Shek, 1998b). Nehlsen-Cannarella et al. (1997) reported that a moderate (10 kg) diet-induced weight loss was sufficient to impair the function of T and B cells, monocytes, and granulocytes.

D. Muscle Injury

The international competitor often develops cumulative subclinical tissue injuries in the working muscles during periods of intensive training These lesions cause local and systemic acute-phase reactions. In the short term, the release of C-reactive protein stimulates the phagocytic action of monocytes. However, the chemotactic migration of leukocytes to injured tissue subsequently may increase vulnerability in other parts of the body, and the generation of reactive species during the repair process may also lead to a suppression of immune function in a manner analogous to that of clinical sepsis (Northoff, Enkel, & Weinstock, 1995).

Support for this last mechanism is provided by studies that show that the administration of vitamin C and other anti-oxidants can protect against exercise-induced infections (Hemilä, 1996; Peters, 1997; Peters-Futre, 1997).

E. Environmental Factors

Immune function is modulated by a variety of environmental stresses such as extremes of heat and cold, high and low ambient pressures, inhalation of polluted air, sleep deprivation, time-zone shifts, and exposure to high and low gravitational forces (Shephard & Shek, 1998c). Relative to the average sedentary person, the active individual has a greater chance of exposure to most of these stresses. For example, many athletes frequently develop quite high core temperatures. Because of solar radiation, heat stress can be much more severe for an athletic competitor than for a laboratory subject, even if both ostensibly perform a comparable amount of physical activity at the same ambient temperature.

Likewise, the inhalation of air polluted by contaminants such as ozone can in itself induce an acute-phase response on the part of alveolar macrophages, and by virtue of the large respiratory minute volume that is sustained over an event, an endurance athlete is at particular risk of such an effect.

The neurohormonal responses to environmental stressors may in themselves have a marked effect on immune function—for example, the catecholamines secreted in response to severe cold, or the cortisol and cytokines (IL-1 and IL-6) associated with a rise in core temperature. Finally, if the individual is not habituated to an unusual environment, it may prove psychologically stressful, with resulting consequences for immune function.

F. Psychological Stressors

Many types of psychological stress, from a first parachute jump to a critical university examination, impair aspects of immune function with an impact upon susceptibility to upper respiratory infections,

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including NK activity, lymphocyte proliferation, and salivary IgA levels (Shephard, 1997).

Vigorous physical activity—especially enforced exercise in animals and competition in humans—induces many of the neurohormonal responses associated with psychological stress, including substantial secretions of epinephrine and norepinephrine, cortisol, and growth hormone. In the competitive athlete, the inherent response to physical activity is supplemented by pressures due to the contest itself; expectations of the coach, sponsors, and general public; and the demands of international travel, including disturbance of circadian rhythms and long periods of absence from a normal home environment.

There have been reports that as much as a quarter of the variance in virus shedding from individuals inoculated with a rhinovirus can be traced to restricted social contacts and an excessive amount of time spent in goal-directed activities (Totman, Kiff, Reed, & Craig, 1980); such a lifestyle has now become almost inevitable during preparation for international athletic competition. All of these various factors increase the likelihood of upper respiratory infection in athletes, particularly around the time of major competition.

VI. PREVENTION OF INFECTION

Given that heavy physical activity can enhance the risk of upper respiratory infection, it is important to stress tactics of prevention, particularly for the competitive athlete. A number of practical measures reduce the likelihood of clinical infection. These include controlling exposure to pathogens, optimizing training and diet, minimizing environmental and psychological stresses, and offering preventive chemotherapy and/or immunotherapy.

A. Control of Exposure

Impairment of immune function sometimes leads to reactivation of a latent Epstein–Barr virus, which is widely prevalent in the young adult population. However, the development of a clinical infection generally involves exposure to an external pathogen.

Where practicable, athletes should avoid contact with young children and others who are showing symptoms of an upper respiratory infection. Hand contact is an important route for the transmission of respiratory viruses. The hands should be washed carefully before food is eaten. Some pathogens can also enter the body via the mucosa of the nose and eyes; neither should be rubbed with dirty hands.

B. Optimizing Training and Diet

Given reports that link impaired immune function to overtraining, any conditioning program should be matched carefully to the individual's initial physical status, and responses should be monitored closely. Declining performance, excessive fatigue, muscle soreness, a depression of mood, and adverse responses to simple psychological tests (such as the Profile of Mood States) are all indications that the intensity of training should be reduced (Shephard & Shek, 1998a).

Given the contribution of nutrition to immune function, it is important to ensure an adequate intake of overall food energy, good-quality protein, and antioxidants. In particular, vitamin C supplements can significantly reduce the incidence, duration, and severity of upper respiratory tract infections in endurance athletes (Hemilä, 1996; Peters, 1997; Peters-Futre, 1997; Shephard & Shek, 1998b). Competitors in a number of sports tend to develop a negative energy balance, particularly if the event demands prolonged physical activity or if performance is judged in part on physical appearance. It is less clear whether the negative energy balance is sufficiently severe to limit immune function. At least in animal studies, food deprivation must be quite severe before immune function deteriorates.

C. Minimizing Environmental and Psychological Stress

Another important preventive tactic is to minimize all forms of stress, not only psychological but also such environmental influences as excessive heat, cold, high altitude exposure, time zone shifts, and sleep deprivation.

D. Chemotherapy and Immunotherapy

Athletes are well advised to update their schedule of inoculations against the viruses prevalent at the venue of a major international competition. If the serum immunoglobulin levels are low, the administration of immunomodulating preparations (including intramuscular injections of human immunoglobulins) may also reduce the severity of disease if not the risk of bronchopulmonary infections (Shephard, 1997). For instance, a German study (Frohlich, Simon, Schmidt, Hitschhold, & Bierther, 1987) found that monthly injections of immunoglobulin led to a threefold reduction in the incidence of infections relative to control subjects. In contrast, world-class canoeists who were given nasal IgA showed no apparent benefit

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relative to controls, but this was perhaps not surprising, since the controls remained healthy and showed no evidence of subnormal levels of IgA (Lindberg & Berglund, 1996).

Intradermal kits (for example, Multitest Merieux, a cocktail of seven common antigens) allow repeated assessments of immunocompetence over the course of training. Salivary or mucosal immunoglobulins also can be monitored, although the link between low immunoglobulin levels and an increased susceptibility to infection remains tenuous.

Given the probable suppression of immune function by prostaglandins, immune function may also be helped by the administration of nonsteroidal anti-inflammatory agents such as indomethacin. Benefit is particularly likely if there is evidence of local muscular inflammation and soreness.

VII. TREATMENT OF INFECTION

Occasional anecdotes tell of athletes achieving their best competitive times despite upper respiratory infections (Eichner, 1993), but generally such episodes cause a deterioration of physical performance. Often, the end result of a minor infection is that the competitor misses either a training session or an actual competition (Weidner, 1994).

Some deterioration of physical performance is to be anticipated as a consequence of systemic infections, given increases in resting core temperature, heart rate, and oxygen consumption and an altered activity of performance-related enzymes in both skeletal and cardiac muscle (Ilbäck, Friman, Crawford, & Neufeld, 1991). Laboratory tests show that infection reduces the time to exhaustion in experimental animals, and in humans, aerobic power and isometric and isokinetic strength all tend to be reduced. Nevertheless, it remains difficult to be certain how far these changes reflect a reduced motivation to maximal effort rather than an inherent effect of the disease process (Shephard, 1997).

In some instances, a postviral fatigue syndrome (Behan, Behan, Gow, Cavanagh, & Gillespie, 1993) may continue to limit both aerobic and anaerobic effort for a year or longer, but normal performance is usually regained quite rapidly once the acute illness has passed.

If an athlete develops an acute infection, it is important for the team physician to determine whether he or she has manifestations of a systemic viral disorder (Eichner, 1993). A simple upper respiratory infection requires no more than some moderation of training, with use of a decongestant by day and an antihistamine at night. However, if competition is approaching, care must be taken to ensure that prescribed medications do not breach antidoping rules. On the other hand, if the individual has developed a systemic viral illness, exercise must be approached with caution. Heavy training or competition can increase the severity of disease, and myocarditis can lead (albeit rarely) to death from cardiac arrest during exercise. Warning signs of systemic infection include fever, myalgia, fatigue, cough, vomiting, diarrhea, and lymphadenopathy. At least for recreational athletes, it is prudent to rest until symptoms of the infection have passed.

VIII. CONCLUSIONS

Both a single bout of exhausting physical activity and very heavy training cause what seem a substantial array of immune disturbances. Further, these changes could reduce resistance to viral infections, in keeping with much of the available epidemiological data. However, interpretation of current findings must remain cautious. There are many possible causes of spurious associations between vigorous physical activity and upper respiratory infection. Moreover, many of the supposedly supporting immunological changes have been observed in specimens of peripheral blood, where changes in cell counts and activity may reflect no more than a demargination of previously sequestered cells, followed by their migration into recently active or injured tissues. There may thus be little true change in either cell count or antiviral activity in the body as a whole.

A further important issue in many acute experiments is that even if immune function has been suppressed, this disturbance has persisted for only a few hours. Exposure to infection would thus need to be closely coincident with the exercise bout if susceptibility to disease were to be increased. Finally, a moderate training program not only enhances resting immune function but also attenuates acute exercise-induced disturbances. Thus, although athletes may show an acute depression of an immune parameter such as NK cell count during or following a bout of intensive exercise, the absolute level of immune function may remain greater than that of sedentary individuals throughout the period of observation.

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